

07/12/90

O N - L I N E T E X T V A L I D A T I O N

PAGE 6

17:17:26

E R R O R R E P O R T

PATENT NO: E:49488059.002

PAGE NO: 4	LINE NO: 82	SECTION COMMAND (+de) OUT OF SEQUENCE !!
PAGE NO: 5	LINE NO: 109	MISSING LIGHT CMND (+1) FOLLOWING (+b) !!

--* NEW PATENT *-*-*

Group A

PATENT # E:49488059.002

0001 ^pg,2

0002 ^su ^cl DESCRIPTION OF THE TECHNICAL FIELD

0003 [p This invention relates to the salt of diclofenac with a cyclic organic
0004 base and to pharmaceutical compositions which contain it.

0005 ^{+pb}
^ More particularly, the invention relates to the salt of diclofenac with
0006 a cyclic organic base in the various pharmaceutical forms, and preferably
0007 in granular form for use in extemporaneous solutions for oral <<<<
>>>>administration.

0008 [p Diclofenac ([b 2[8 2,6^1 -dichlorophenyl)-amino[9 benzeneacetic <<<<
>>>>acid) is an anti-inflammatory

0009 medicament which has been known for a considerable time and
0010 which together with numerous other compounds falls under the general <<<<
>>>>formula

0011 of U.S. Pat. No. ^b 3,558,690.

0012 [p One of the characteristics of these compounds is that they cyclize <<<<
>>>>in an

0013 acid environment to give the corresponding indolinones. In order to obtain
0014 stabilization of the open form, they are salified with non-toxic organic
0015 or inorganic bases as described for example in the aforesaid patent.
0016 However, in this patent no information is given regarding the solubility
0017 of said salts in water, and notwithstanding the fact that several years
0018 have passed since the teachings of the said patent were made available,
0019 no aqueous pharmaceutical composition of diclofenac has been marketed.

0020 ^cl BRIEF SUMMARY OF THE INVENTION

0021 [p We have now found that it is possible to obtain a highly water soluble
0022 diclofenac salt by salifying diclofenac with a cyclic organic base having
0023 the general formula (I)

0024 ^t,0020

0025 [ps in which X is a group of the formula (CH^hd 2^1) [hd m[1 , in <<<<

>>>>which m is ^b 0 ^1 or ^b 1 ^1 or ^b 2, [1

0026 ^pg,3

0027 or X is oxygen or S or NR, in which R is an alkyl group C[hd 1^1 [14 <<<<
>>>>C^hd 4^1 , and n

0028 is ^b 2 ^1 or ^b 3. ^1 This is very surprising in the light of the <<<<
>>>>fact that U.S.

0029 Pat. No. ^b 3,558,690 ^1 comprises salts of diclofenac with bases <<<<
>>>>such as ^b

0030 2^1 -aminoethanol

0031 and pyrrolidine which are very close to the bases of the formula

0032 (I) from a structural viewpoint, whereas these salts are practically
0033 insoluble in water.

0034 [p In contrast to the tablet form currently used for oral administration
0035 one particular unforseeable advantage of the salt of diclofenac with a
0036 base of formula (I) is that when prepared in granular form and stored
0037 in water-impermeable sachets, it enables extemporaneous aqueous solutions
0038 to be prepared which while totally maintaining their activity level do
0039 not give rise to gastrolesion.

0040 [p The enormous advantage of such a behaviour which obviates any risk to
0041 the patient ingesting the medicament is an obvious considerable merit
0042 in terms of its pharmaceutical application.

0043 [p The salt of diclofenac with a base of formula (^b 1^1) therefore <<<<
>>>>constitutes

0044 a subject of the present invention, a further subject of the invention
0045 being pharmaceutical compositions containing a therapeutically
0046 useful dosage of said salt.

0047 [p The process for preparing this salt is extremely simple from an <<<<
>>>>industrial

0048 viewpoint, it being characterized by dissolving diclofenac in a
0049 suitable organic solvent, adding a base of formula (I), reacting said

0050 compounds together at ambient temperature, removing the solvent and
0051 crystallising the product obtained.

0052 ^de ^cl DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

0053 [p Suitable organic solvents for dissolving diclofenac are acetone, <<<<
>>>>ethanol

0054 and chloroform. The base used in equimolar quantity or in slight
0055 excess with respect to the diclofenac. The reaction is conducted at
0056 ambient temperature under agitation for a time of between ^b 0³5 ^1 <<<<
>>>>and ^b 3 ^1

0057 hours. The solvent is removed by distillation under vacuum at a <<<<
>>>>temperature

0058 of between ^b 35^1 [20 [0 and ^b 45^1 ^20 ^0 C. The salt is <<<<
>>>>crystallised by treating the

0059 distillation residue with hexane or petroleum ether under energetic <<<<
>>>>agitation.

0060 ^pg, 4

0061 The unrefined salt obtained is redissolved in acetone and recrystallised
0062 from hexane or petroleum ether.

0063 ^{+pb} The solubility characteristics of the salt of diclofenac with hydroxy-
>>>>ethylpyrrolidine (ID) and

0064 with hydroxyethylpiperidine (IP) compared with
0065 the salts of diclofenac with sodium (SD), with pyrrolidine (PD) and with
0066 [b 2[1 -aminoethanol (AD) are given in the following table.

0067 ^t, 0040

0068]p The salt of diclofenac with a base of formula (I) also has high <<<<
>>>>shelf-life.

0069 The pharmaceutical compositions according to the present invention <<<<
>>>>contain

0070 a therapeutically active quantity of the salt of diclofenac with a
0071 base of formula (I) together with pharmaceutically acceptable liquid or
0072 solid excipients of organic or inorganic type, and can be administered
0073 orally. Preferably, said compositions contain an active ingredient <<<<
>>>>quantity

0074 corresponding to ^b 10^14 200 ^l mg of diclofenac per unit dosage.

0075 ^{+pb} Examples of preferred pharmaceutical forms are granular forms packaged in
0076 sachets of water-impermeable material, and are dissolved in a little <<<<
>>>>water

0077 to form solutions for oral administration.

0078 [p In addition to the excipients, said compositions can contain <<<<
>>>>preservatives,

0079 stabilizers, wetting agents, emulsifiers, osmotic pressure regulating
0080 salts, buffers, dyestuffs, sweeteners and flavorings. They are prepared
0081 by known methods and can contain other therapeutic agents.

0082 [de [p The following examples are described by way of non-limiting <<<<

>>>>illustration

0083 of the present invention.

0084 ^c1 EXAMPLE ^b 1

0085 [c1 Preparation of the salt of diclofenac with hydroxyethylpyrrolidine

0086 [p ^b 14.75 ^1 g (^b 49.8 ^1 mmols) of ^b 2^1 -[8 (^b 2,6^1 -<<<<

>>>>dichlorophenyl)-amino[9 benzeneacetic

0087 acid (diclofenac) were dissolved in acetone (^b 50 ^1 ml), and ^b <<<<

>>>>5.75 [1 g ([b 49.9 [1

0088 ^pg,5

0089 mmoles) of freshly distilled hydroxyethylpyrrolidine were added to the
0090 solution obtained.

0091 [p After keeping the solution under agitation for one hour at ambient <<<<
>>>>temperature,

0092 the solvent was removed under vacuum at ^b 40^1 ^20 ^0 C.

0093 [p The oily residue was treated with hexane (^b 100 ^1 ml) and the <<<<
>>>>obtained mixture

0094 kept under energetic agitation until the oil was transformed into a
0095 crystalline solid, which was separated by filtration and dried. ^b 17 <<<<
>>>>^1 g of

0096 product were obtained having an M.P. of ^b 57[20 [14 58[1 [20 [0 C. <<<<
>>>>(yield ^b 83[1 % of theoretical).

0097 [p The unrefined product obtained in this manner was dissolved in acetone
0098 (^b 50 ^1 ml), decolorized with animal charcoal and filtered. The solution
0099 was evaporated under vacuum, and the residue treated with hexane as
0100 described heretofore. The salt of diclofenac with hydroxyethylpyrrolidine
0101 was obtained in its pure state, with an M.P. of ^b 97.5^20 [14 100^1 <<<<
>>>>^20 ^0 C.

0102 ^cl EXAMPLE ^b 2

0103 ^cl Preparation of the salt of Diclofenac with ^b 1^1 -(^b 2^1 -<<<<
>>>>hydroxyethyl)-piperidine

0104 [p A solution of ^b 8.9 ^1 g of ^b 2^1 --/ (^b 2,6^1 -dichloro-phenyl)-<<<<
>>>>amino[9 -phenylactic acid

0105 in ^b 220 ^1 ml of ethyl acetate is treated with a solution of ^b <<<<
>>>>3.88 ^1 g of ^b 1^1 -(^b 2^1 -hydroxyethyl)-piperidine

0106 in ^b 20 ^1 ml ethyl acetate while stirring.

0107 [p After ^b 30 ^1 minutes the clear solution is concentrated under <<<<
>>>>reduced pressure

0108 to a volume of 10^{-1} ml and diluted with 100^{-1} ml diethyl <<<<
>>>>ether. The

0109 crystalline 1^{-1} - (2^{-1} -hydroxyethyl)-piperidine salt of 2^{-1} -[8^{0+/-} <<<<
>>>>([2,6[1 -dichlorophenyl)-amino[9 -phenylacetic

0110 acid precipitates and is filtered off.

0111 M.P. $109[20[14[11^{-1} 20$; solubility in water: 20^{-1} % w/v.

0112 cl EXAMPLE [b 3

0113 [cl Preparation of a granulate containing the salt of diclofenac with <<<<
>>>>hydroxyethylpyrrolidine

0114 [p A granulate was prepared having the following composition:

0115 $t, 0050$

0116 ^pg, 6

0117 [p ^b 70 ^l g of the salt of diclofenac with hydroxyethylpyrrolidine, <<<<
>>>>^b 1.7^l ^b 98 ^l Kg

0118 of sorbitol and ^b 50 ^l g of aspartame were mixed together in a <<<<
>>>>steel cube

0119 mixer for ^b 20 ^l minutes.

0120 [p ^b 150 ^l g of polyethyleneglycol ^b 6000, 1 ^l g of E ^b 124 ^l <<<<
>>>>and ^b 1 ^l g of E ^b 110 ^l HC were

0121 dissolved in ^b 280 ^l ml of boiling water under agitation.

0122 [p The solid mixture and solution prepared in this manner were mixed <<<<
>>>>together

0123 in a fluidized bed granulator using ^b 100 ^l ml of mixing water. The
0124 granulate obtained in this manner was sieved through an oscillating
0125 screen with a mesh size of ^b 1 ^l mm.

0126 [p ^b 130 ^l g of flavoring was sieved separately with the same <<<<
>>>>screen, and was

0127 mixed with the said granulate in a cube mixer for ^b 20 ^l minutes.

0128 [p The granulate obtained in this manner was dispensed into sachets of
0129 water-impermeable material, dispensing ^b 2,2 ^l g of granulate into each
0130 sachet.

0131 [p At the moment of use, the contents of each sachet were easily dissolved
0132 in a little water to form a drinkable solution which in terms of acid
0133 contains ^b 50 ^l mg of diclofenac.

0134 ^cm We claim:

0135 ^pg,7

0136 ^cm 1. A water soluble salt, comprising:

0137 [p1 diclofenac ([b 2[1 -[8 (-[b 2,6[1 -dichlorophenyl)-amino-[9

0138 benzeneacetic acid); and

0139 [p1 a cyclic organic base having the formula

0140 [t,0070

0141 [p1 wherein n is [b 2.

0142 ^pg, 8

0143 ^cm 2. A pharmaceutical composition comprising a

0144 therapeutically active quantity of a water soluble salt of

0145 diclofenac and a cyclic organic base having the formula

0146 [t,0080

0147 [p1 wherein n is [b 2[1 , together with a pharmaceutically

0148 acceptable excipient.

0149 ^cm 3. The composition of claim 2, wherein a quantity of

0150 the salt of diclofenac and said cyclic organic base corresponding

0151 to [b 10[14 200 [1 mg of diclofenac per unit dosage is present.

0152 ^cm 4. The composition of claim 2, wherein said composition

0153 is in granular form and is packaged in a water-impermeable

0154 sachet.